TEST PLAN
(Revised)

For

2,2-Bis(bromomethyl)-1,3-propanediol

CAS No. 3296-90-0

U.S. EPA HPV Chemical Challenge Program Submission

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By

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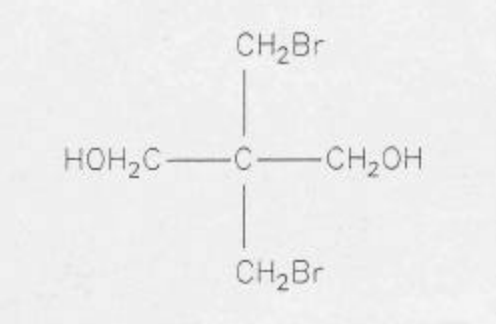
Test Plan (Revised) for 2,2-Bis(bromomethyl)-1,3-propanediol (CAS No. 3296-90-0)

1. General Information

1.1 CAS Number: 3296-90-0

1.2 Molecular Weight: 261.9

1.3 Structure and formula: $C_5H_{10}Br_2O_2$



1.4 Commercial Applications

2,2-Bis(bromomethyl)-1,3-propanediol is used as a reactive flame retardant in unsaturated polyester resins, in moulded products and in rigid polyurethane foam.

1.5 Worker/consumer exposure

Workers involved in both the manufacture of 2,2-Bis(bromomethyl)-1,3-propanediol and of product containing the chemical are likely to have minimal exposure to the chemical as it is expected that good industrial hygiene practices will be followed and personal protective equipment worn to minimise exposure.

There are no direct consumer applications and therefore no direct sales to the general public. The most likely source of consumer exposure to 2,2-Bis(bromomethyl)-1,3-propanediol is through fugitive dust from products containing the chemical.

Its use as a reactive flame retardant means that 2,2-Bis(bromomethyl)-1,3-propanediol is chemically bonded with the polymer molecules and is unlikely to be released into the environment in the form of the parent compound and, consequently, is unlikely to exert toxicity associated with the parent compound and be a risk to the environment or consumers.

2. Review of Existing Data and Development of Test Plan

AmeriBrom, Inc. has undertaken a comprehensive evaluation of all relevant data on the SIDS endpoints of concern for 2,2-Bis(bromomethyl)-1,3-propanediol.

The availability of the data on the specific SIDS endpoints is summarized in Table 1. Table 1 also shows data gaps that will be filled by additional testing.

Table 1 - Available Adequate Data and Proposed Testing

2,2-Bis(bromomethyl)-1,3-propanediol CAS No. 3296-90-0	Information Available?	GLP	OECD Study?	Other Study?	Estimation Method?	Acceptable?	SIDS Testing required?
Endpoint / Study	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N
Physical / Chemical Elements							
1. Melting point	Y	?		Y		Y	N
2. Boiling point	N					N	Y
3. Vapor pressure	Y	N			Y	N	Y
4. Partition coefficient (K_{ow})	Y	?		Y	Y	Y	N
5. Water solubility	N			Y	Y	N	Y
Environmental Fate & Pathway							
6. Photodegradation	N				Y	Y	N
7. Stability in water (Hydrolysis)	N				N	N	Y
8. Transport and distribution between environmental compartments (Fugacity)	N					N	Y
9. Biodegradation	Y	?		Y		Y	N
Ecotoxicology							
10. Acute toxicity to fish	N					N	Y
11. Acute toxicity to algae	N					N	Y
12. Acute toxicity to Daphnia	N					N	Y
Health Elements							
13. Acute toxicity	Y	Y	Y	Y		Y	N
14. Genetic toxicity in vivo (chromosomal aberrations)	Y	?	N	Y		Y	N
15. Genetic toxicity in vitro (gene mutations)	Y	Y	Y	Y		Y	N
16. Repeat dose toxicity	Y	Y	Y	Y		Y	N
17. Reproductive toxicity	Y	Y	N	Y		Y	N
18. Developmental toxicity/teratogenicity	N			Y		?	N

A. Evaluation of Existing Physical / Chemical Data Elements and Proposed Testing

1. Melting Point

The melting point of 2,2-Bis(bromomethyl)-1,3-propanediol has been reported as 111-113°C in a peer reviewed publication. No testing will be done for this endpoint.

2. Boiling Point

No adequate data exists. The boiling point of 2,2-Bis(bromomethyl)-1,3-propanediol will be determined using OECD Method 103.

3. Vapor Pressure

At 25 °C the vapor pressure of 2,2-Bis(bromomethyl)-1,3-propanediol is estimated to be 6.4×10^{-6} mm Hg (8.6×10^{-4} Pa) using MPBPWIN v1.40 (EPIWIN modelling program). As this value is greater than the maximum acceptable calculated vapor pressure permitted under OECD TG 104 [8×10^{-8} mm Hg (1×10^{-5} Pa)], the vapor pressure will be determined experimentally using OECD Method 104.

4. Partition Coefficient

The partition coefficient (i.e. K_{ow} or P_{ow}) for 2,2-Bis(bromomethyl)-1,3-propanediol has been reported as Log P_{ow} = 2.29 and 1.06 in two peer reviewed publications. The second reported value of 1.06 is close to the value of 0.85 estimated by KOWWIN v1.66 (EPIWIN modelling program). No testing will be done for this endpoint.

5. Water solubility

The water solubility for 2,2-Bis(bromomethyl)-1,3-propanediol has been reported as 3.8 $X10^4$ mg/L in a peer reviewed publication. This reported value of 3.8 $X10^4$ mg/L is an order of magnitude greater than the 2524 mg/L estimated by WSKOWWIN v1.40 (EPIWIN modelling program). The water solubility of 2,2-Bis(bromomethyl)-1,3-propanediol will therefore be determined using OECD Method 105.

Summary of Physicochemical Properties Testing: The boiling point (OECD 103), water solubility (OECD 105) and vapor pressure (OECD 104) of 2,2-Bis(bromomethyl)-1,3-propanediol will be determined. Existing data for melting point, and partition coefficient are considered adequate to fill their respective endpoints.

B. Evaluation of Existing Environmental Fate & Pathway Data Elements and Proposed Testing

6. Photodegradation

The direct photolysis photodegradation Half-life ($t_{½}$) of 2,2-Bis(bromomethyl)-1,3-propanediol is estimated to be 14.32 Hrs (12-Hr Day, 1.5 x 10^6 OH radicals/cm^3) by AOPWIN v1.90 (EPIWIN modelling program). This estimate is considered adequate to fill the data requirements for this endpoint and no testing will be conducted for this end point at this time.

7. Stability in Water (Hydrolysis)

No adequate data could be found or estimated for this endpoint, therefore the stability in water of 2,2-Bis(bromomethyl)-1,3-propanediol will be determined using OECD Method 111.

8. Transport and Distribution between Environmental Compartments (Fugacity)

No adequate data could be found for the transport and distribution between environmental compartments of 2,2-Bis(bromomethyl)-1,3-propanediol, therefore the data will be estimated using the Mackay Level III Fugacity Model.

9. Biodegradation

2,2-Bis(bromomethyl)-1,3-propanediol has been shown to be not readily biodegradable (3-33% by BOD after 28 days) in a peer-reviewed study conducted using a Japanese MITI test. This data is considered adequate to meet the data requirements for this endpoint and no testing will be conducted for this endpoint at this time.

Summary of Environmental Fate & Pathway Testing: The stability in water (hydrolysis) of 2,2-Bis(bromomethyl)-1,3-propanediol will be determined by OECD Method 111. Transport and distribution between environmental compartments (Fugacity) will be estimated using the Mackay Level III Fugacity Model. The existing data for photodegradation and biodegradability is considered adequate to fill the data needs for those endpoints at this time.

C. Evaluation of Existing Ecotoxicity Elements Data and Proposed Testing

10. Acute Toxicity to Fish

The acute toxicity of 2,2-Bis(bromomethyl)-1,3-propanediol to fish will be determined using OECD Method 203.

11. Acute Toxicity to Algae

The acute toxicity of 2,2-Bis(bromomethyl)-1,3-propanediol to algae will be determined using OECD Method 201.

12. Acute Toxicity to Daphnia

The acute toxicity of 2,2-Bis(bromomethyl)-1,3-propanediol to daphnia will be determined using OECD Method 202, part 1.

Summary of Ecotoxicity Testing: The acute toxicity of 2,2-Bis(bromomethyl)-1,3-propanediol to fish (OECD 203), algae (OECD 201) and daphnia (OECD 202, part 1) will be determined.

D. Evaluation of Existing Health Elements Data and Proposed Testing

13. Acute Toxicity

Acute Oral Toxicity

The acute oral toxicity has been determined in two studies. The first study (OECD 401, rat, GLP) reported an LD50 value of > 2000 mg/kg bw. The second study (method unclear, rat, no GLP), conducted using technical grade material, reported an LD50 value of 1880 mg/kg bw.

Skin Irritation

This non-SIDS endpoint has been evaluated using a commercial grade of 2,2-Bis(bromomethyl)-1,3-propanediol in a rabbit skin irritation test (U.S. Federal Register, §191.11, 1964). The substance was classified as mildly irritating to skin.

Eye Irritation

This non-SIDS endpoint has been evaluated using a commercial grade of 2,2-Bis(bromomethyl)-1,3-propanediol in a test using New Zealand White rabbits (U.S. Federal Register, §191.12, 1964). The substance was classified as an eye irritant.

This data is considered adequate to meet the data requirements for the acute toxicity endpoint and no testing will be conducted for this endpoint at this time.

14. Genetic toxicity in vivo (chromosomal aberrations)

The results of an in vivo mouse bone marrow micronucleus study using male mice was equivocal, but in a second study 2,2-Bis(bromomethyl)-1,3-propanediol was found to induce micronuclei in the bone marrow of female mice. In a mouse peripheral blood micronucleus test, performed using animals from the 13-week repeat dose study, 2,2-Bis(bromomethyl)-1,3-propanediol caused significant increases in micronucleated normochromatic erythrocytes in males and females. In an in vitro cytogenetic assay 2,2-Bis(bromomethyl)-1,3-propanediol induced chromosomal aberrations in Chinese hamster ovary (CHO) cells in the presence of rat S-9 mix.

This data is considered adequate to meet the data requirements for the genetic toxicity in vivo (chromosomal aberrations) endpoint and no testing will be conducted for this endpoint at this time.

15. Genetic toxicity in vitro (gene mutations)

Three grades of 2,2-Bis(bromomethyl)-1,3-propanediol (Commercial, 98.63% and 99.5%) have been tested for potential genotoxicity in the Ames Salmonella assay (OECD 471, strains TA1535, TA1537, TA98 and TA100, GLP). In each case, there was no evidence of mutagenic activity in the presence or absence of metabolic activation with rat S-9 mix, however there was clear evidence of mutagenic activity in strains TA1535 and TA100 in the presence of metabolic activation with hamster S-9 mix. A further, unreliable, study using lower concentrations of test substance also gave negative results in the presence and absence of metabolic activation using rat S-9 mix. 2,2-Bis(bromomethyl)-1,3-propanediol did not induce sister chromatid exchanges when tested using Chinese hamster ovary cells, either with or without metabolic activation using rat S-9 mix.

This data is considered adequate to meet the data requirements for the genetic toxicity in vitro (gene mutations) endpoint and no testing will be conducted for this endpoint at this time.

16. Repeat Dose Toxicity

Two repeat dose studies have been conducted under the National Toxicology Program using F344/N rats and B6C3F_1 mice. In a 13-week study, NOEL values of 1250 ppm (rats) and 625 ppm (male mice) were obtained. A NOEL value for female mice was not achieved. Dose-related effects seen were reduced body weight (rats/mice) and hypoactivity and abnormal posture (mice). Chemical-related lesions were observed only in the urinary bladder and kidney of rats and mice. Kidney lesions in mice (papillary necrosis and renal tubule regeneration fibrosis) were more severe than those observed in rats (papillary degeneration). Urinary bladder lesions in the mice were also more severe than in rats. In a 2-year study, NOAEL values were not achieved. LOAEL values of 2500 ppm (rats) and 312 ppm (mice) were obtained. Dose related effects included reduced body weight in rats, skin and subcutaneous tissue masses on the face, tail and the ventral and dorsal surfaces of rats and swelling, discharge and tissue masses involving the eye in mice. Survival of rats and mice was significantly reduced. This reduction was attributed primarily to the carcinogenic effects of the chemical. Numerous neoplasms were present in both rats and mice. Based on these studies, it was concluded that there was clear evidence of carcinogenic activity in male and female F344/N rats and B6C3F_1 mice.

This data is considered adequate to meet the data requirements for the repeat dose toxicity endpoint and no testing will be conducted for this endpoint at this time.

17. Reproductive Toxicity

The reproductive toxicity of 2,2-Bis(bromomethyl)-1,3-propanediol in CD-1 mice has been evaluated in a 2-generation, GLP study using the NTP Fertility Assessment by Continuous Breeding (FACB) system. In both the F_0 and F_1 studies, NOEL (adult) = 0.1%, NOEL (offspring) = 0.1%. When administered at the highest dose level (0.4%), reproduction was adversely affected. A cross over mating study showed that it was the reproductive performance of females that was adversely affected. Continued treatment resulted in a significant drop in body weight. The reproductive performance of second generation mice was adversely affected, with respect to the number of live pups per litter and the adjusted live pup weight.

The observation of reproductive effects at dose levels that were toxic to the adult parents and a clear NOEL suggests that there is no serious reproductive risk associated with exposure to the test material below the threshold of adult toxicity.

It is considered that the elements of the NTP fertility assessment by continuous breeding study are sufficient to provide a reasonable assessment of the hazard to reproduction of 2,2-Bis(bromomethyl)-1,3-propanediol and that further screening level studies are not required.

18. Developmental Toxicity / Teratogenicity

The above NTP Fertility Assessment by Continuous Breeding (FACB) study of 2,2-Bis(bromomethyl)-1,3-propanediol in CD-1 mice assessed many of the same parameters that are measured during a developmental toxicity study. These parameters included survival rates, litter size, litter weights, sex and sex ratios, weight gain of pups, number of pups with grossly visible abnormalities and effects on offspring. However the number of implantations, number of corpora lutea, number aborting and number of resorptions, as well as other critical parameters necessary to fully assess the developmental toxicity potential of 2,2-Bis(bromomethyl)-1,3-propanediol were not measured.

The observation of no gross developmental effects in offspring, not related to lack of weight gain or survival, at dose levels that were toxic to the adult and a clear NOEL suggests that there may be no serious developmental toxicity risk associated with exposure to the test material below the threshold of adult toxicity. Given that this substance has also been shown to induce lesions in both sexes in several repeat dose studies, controlling exposures to reduce the risk of a carcinogenic effect should adequately protect against any subtle developmental effect.

It is considered that the elements of the NTP fertility assessment by continuous breeding study are sufficient to provide a reasonable screening level assessment of the developmental toxicity hazard of 2,2-Bis(bromomethyl)-1,3-propanediol and that further screening level studies for developmental toxicity are not required at this time.

Summary of Health Elements Data and Proposed Testing: All health effects endpoints have been adequately addressed and no new health elements testing is to be under taken at this stage of the screening level process.

3. Evaluation of Data for Quality and Acceptability

The collected data were reviewed for quality and acceptability following the general US EPA guidance (5.) and the systematic approach described by Klimisch et al (6.). These methods include consideration of the reliability, relevance and adequacy of the data in evaluating their usefulness for hazard assessment purposes. This scoring system was only applied to ecotoxicology and human health endpoint studies per EPA recommendation (7.).

The codification described by Klimisch specifies four categories of reliability for describing data adequacy. These are:

(1) Reliable without restriction: Includes studies or data complying with Good Laboratory Practice (GLP) procedures, or with valid and/or internationally accepted testing guidelines, or in which the test parameters are documented and comparable to these guidelines.

(2) Reliable with Restrictions: Includes studies or data in which test parameters are documented but vary slightly from testing guidelines.

(3) Not Reliable: Includes studies or data in which there are interferences, or that use non-relevant organisms or exposure routes, or which were carried out using unacceptable methods, or where documentation is insufficient.

(4) Not Assignable: Includes studies or data in which insufficient detail is reported to assign a rating, e.g. listed in abstracts or secondary literature.

4. References

1. MPBPWIN v1.40. EPIWIN Modelling Program. Meylan, W. & Howard, P. (2000), Syracuse Research Corporation, Environmental Science Center, 6225 Running Ridge Road, North Syracuse, NY 13212-2510

2. KOWWIN v1.66. EPIWIN Modelling Program. Meylan, W. & Howard, P. (2000), Syracuse Research Corporation, Environmental Science Center, 6225 Running Ridge Road, North Syracuse, NY 13212-2510

3. WSKOWWIN v1.40. EPIWIN Modelling Program. Meylan, W. & Howard, P. (2000), Syracuse Research Corporation, Environmental Science Center, 6225 Running Ridge Road, North Syracuse, NY 13212-2510

4. AOPWIN v1.90. EPIWIN Modelling Program. Meylan, W. & Howard, P. (2000), Syracuse Research Corporation, Environmental Science Center, 6225 Running Ridge Road, North Syracuse, NY 13212-2510

5. USEPA (1998). Guidance for Meeting the SIDS Requirements (The SIDS Guide). Guidance for the HPV Challenge Program. Dated 11/2/98.

6. Klimisch, H. J., et al (1997). A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data. Regul. Toxicol. Pharmacol. 25:1-5

7. USEPA (1999). Determining the Adequacy of Existing Data. Guidance for the HPV Challenge Program. Draft dated 2/10/99.